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10/088,202	03/15/2002	Eun Jeong Park	58049-00003	1462

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EXAMINER	
FORD, VANESSA L	
ART UNIT	PAPER NUMBER
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/088,202	PARK ET AL.	
	Examiner	Art Unit	
	VANESSA L. FORD	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *3-5,7-11,15-17,19 and 20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,6,12-14 and 18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 March 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/19/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is responsive election of Group I, claims 1-2, 6, 14 and 18 with traverse filed March 21, 2005.

The traversal was on the grounds that Domenighini et al *(EP 0 620 850 B1, March 3, 1999)* do not teach a detoxified protein having an amino acid sequence of heat labile enterotoxin of *E. coli* in which serine at position 63 is substituted with tyrosine. Applicant urges that the claimed invention is novel over Domenighini et al.

Applicant urges that Groups I-IV are linked by a special technical feature and form a single inventive concept. Applicant urges that all of the claims should be examined together.

The special technical feature of Group I is a detoxified protein. The special technical feature lacks novelty under PCT Article 33(2) as anticipated by Domenighini et al, *(EP 0 620 850 B1 published March 3, 1999).* Domeninghini et al teach detoxified proteins of cholera toxins or heat labile toxins produced by *E. coli* which have a substitution at amino acid 63. Domeninghini et al also teach mutations at positions 110 and 112. See page 4. Claim 1 is directed to detoxified and immunogenically active protein having an amino acid sequence of heat-labile enterotoxin of *E. coli,* wherein serine residue at position 63 is substituted with tyrosine or *positions 110 and 112 are mutated in a site-directed manner.* Thus, Domeninghini et al anticipate claim 1 and Group I is the main invention in this application and it lacks novelty, therefore the other claims are not so linked by a special technical feature within the meaning of PCT Rule 13.2 so as to form a single inventive concept. Inasmuch as, the technical feature

does not define a contribution over the art, it is not "special" within the meaning of PCT Rule 13.2. Consequently, Groups I, II and III lack unity of invention.

After reconsideration, Group IV, claims 12 and 13 will be examined with Group I.

Claims 1-8, 11-12 and 14 have been amended.

Claims 3-5, 7-11, 15-17 and 19-20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on March 21, 2005.

Claims 1-2, 6, 12-13, 14 and 18 are under examination.

Claim Objections

2. Claim is objected to for the following informality: claim 1 recites *E. coli* and should recite *Escherichia coli* at the first occurrence in the claims. Correction is required.

3. Claim 2 recites "(SEQ ID No:3)". If Applicant intends that an amino acid in which the serine at position 63 is substituted for tyrosine is SEQ ID No.3, then the recitation "(SEQ ID No:3)" should be positively recited in the claims and not recite with parentheses. Correction is required.

4. Claim 6 recites "(SEQ ID No:5)". If Applicant intends that an amino acid in which the serine at position 63 is substituted for tyrosine is SEQ ID No.5, then the recitation "(SEQ ID No:5)" should be positively recited in the claims and not recite with parentheses. Correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement Regarding the Vaccine

5. Claim 12 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Independent claim 12 is directed to diarrheal vaccine comprising an active ingredient of the detoxified and immunologically active protein of claim 1 and pharmaceutically acceptable carrier.

The instant specification teaches administration of LTS63Y and LTΔ110/112 to mice. See Examples 3-1 to 3-2. The specification teach that mice were immunized intranasally by co-administration of urease antigen and LTS63Y showed high levels of mucosal and systemic anti-urease responses including urease-specific secretary IgA,

serum IgG and IgA antibodies which were equivalent to the responses observed when wild-type LT was used as an adjuvant. See page 22.

The specification does not provide evidence that the claimed vaccines are capable of inducing protective immunity. This demonstration is required for the skilled artisan to be able to use the claimed vaccines for their intended purpose of treating *Escherichia coli* infections. Without this demonstration, the skilled artisan would not be able to reasonably predict the outcome of the administration of the claimed vaccines, i.e. would not be able to accurately predict if protective immunity has been induced. The specification further does not disclose what mode of administration can be used in regard to the vaccines to be capable of reaching the target organs necessary to treat any particular *Escherichia coli* infection.

The ability to reasonably predict the capacity of a single bacterial immunogen or combinations of immunogens to induce protective immunity from *in vitro* antibody reactivity studies is problematic The ability to reasonably predict the capacity of a single bacterial immunogen or combinations of immunogens to induce protective immunity from *in vitro* antibody reactivity studies is problematic. Ellis *(Vaccines, W.B. Saunders Company, 1988, Chapter 29)* exemplifies this problem in the recitation that "the key to the problem (of vaccine development) is the identification of a protein component of a virus or microbial pathogen that itself can elicit the production of protective antibodies"(page 572, second full paragraph). Unfortunately, the art is replete with instances where even well characterized antigens that induce an *in vitro* neutralizing antibody response fail to elicit *in vivo* protective immunity. Boslego et al (*Vaccines and*

Immunotherapy, Pergaman Press, 1991, Chapter 17) teach a single gonococcal pillin protein wherein the protein fails to elicit protective immunity even though a high level of serum antibody response is induced (page 212, bottom of column 2). Accordingly, the art indicates that it would require undue experimentation to formulate and use a successful vaccine without the prior demonstration of vaccine efficacy.

Factors to be considered in determining whether undue experimentation is required, are set forth in In re Wands 8 USPQ2d 1400. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Applying the above test to the facts of record, it is determined that 1) no declaration under 37 C.F.R. 1.132 or other relevant evidence has been made of record establishing the amount of experimentation necessary, 2) insufficient direction or guidance is presented in the specification with respect to developing a vaccine that would achieve a desire level of success when administered to a patient with a bacterial infection that is capable of preventing that bacterial infection, 3) there are no working examples which suggest the desired results of a vaccine against *Escherichia coli* infection used to prevent against *Escherichia coli* infections and 4) the relative skill of those in the art is commonly recognized as quite high (post - doctoral level), and the lack of predictability in the field to which the invention pertains is recognized in the art as evidenced by the cited prior art.

In view of all of the above, in view of the lack of predictability in the art, it is determined that it would require undue experimentation to make and use the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claim 1 is rejected under 35 USC 112 second paragraph for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 recites "positions 110 and 112 are mutated in a site-directed manner". It is unclear as how the amino acids are treated? Are they deleted or substituted? Clarification/correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1-2, 6, 12-14 and 18 are rejected under 35 U.S.C. 102(a) as anticipated by Park et al *(Experimental and Molecular Medicine, June 1999, Vol.31, No. 2, p. 101-107)*.

Independent claim 1 is directed to a detoxified and immunogenically active protein having an amino acid sequence of heat-labile enterotoxin of E. coli, wherein serine residue at position 63 is substituted with tyrosine or positions 110 and 112 are mutated in a site-directed manner.

Independent claim 6 a detoxified and immunogenically active protein having an amino acid sequence of heat-labile enterotoxin of E. coli (SEQ ID NO:5) in which glutamic acid residues at positions 110 and 112 are deleted.

Independent claim 12 is directed to diarrheal vaccine comprising an active ingredient of the detoxified and immunologically active protein of claim 1 and pharmaceutically acceptable carrier.

Independent claim 13 is directed to a mucosal adjuvant comprising an active ingredient detoxified and immunologically active protein of claim 1.

Park et al teach two novel nontoxic mutants of Escherichia coli heat-labile enterotoxin (see the Title and Abstract). Park et al teach an *E. coli* heat labile mutant that has at position 63 a substitution of serine to tyrosine (see the Abstract). Park et al an *E. coli* heat labile mutant that has positions the glutamic acid at positions 110 and 112 deleted (see the Abstract). Park et al teach that antigens were resuspended in PBS buffer containing $NaHCO_3$ and delivered to mice (page 103). The term "vaccine" is being viewed as a term of intended use. Park et al teach that *Escherichia coli* heat-labile enterotoxins are the most potent mucosal adjuvants known to date (page 101). SEQ ID Nos. 3 and 5 would be inherent in the teachings of the prior art. SEQ ID NO.3 corresponding to the *E. coli* heat labile mutant comprising the substitution of serine for

tyrosine at position 63 and SEQ ID NO:5 corresponding to the *E. coli* heat labile mutant comprising the deletions of glutamic acid at positions 110 and 112. Peak et al anticipate the claimed invention.

8. Claim 1 is rejected under 35 U.S.C. 102(b) as anticipated by *(EP 0 620 850 B1 published March 3, 1999).*

Independent claim 1 is directed to a detoxified and immunogenically active protein having an amino acid sequence of heat-labile enterotoxin of E. coli, wherein serine residue at position 63 is substituted with tyrosine or positions 110 and 112 are mutated in a site-directed manner.

Domeninghini et al teach detoxified proteins heat labile toxins produced by *E. coli* which have mutations at positions 110 and 112. See page 4. Thus, the prior art teach positions 110 and 112 are mutated in a site-directed manner. Domeninghini et al anticipate the claimed invention.

Status of Claims

9. No claims allowed.

Conclusion

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to VANESSA L. FORD whose telephone number is (571)272-0857. The examiner can normally be reached on 9 am- 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Mondesi can be reached on (571) 272-0756. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Vanessa L. Ford/
Examiner, Art Unit 1645
April 25, 2009